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| 09/257,650 | 02/25/1999 | MASAHIKO FUJINO | 48194 | 2632 |

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DIKE, BRONSTEIN, ROBERTS & CUSHMAN
130 WATER STREET
BOSTON, MA 02109

| EXAMINER |
|---|
| O HARA, EILEEN B |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | 20 |

DATE MAILED: 02/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/257,650 | FUJINO, MASAHIKO | |
| | Examiner | Art Unit | |
| | Eileen B. O'Hara | 1646 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 December 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14,16-19,21-24 and 26-38* is/are pending in the application.

4a) Of the above claim(s) *1-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14, 16-19, 21-24 and 26-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-14,16-19,21-24 and 26-38* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. Claims 1-14, 16-19, 21-24 and 26-38 are pending in the instant application. Claims 14, 16, 17, 19, 21 and 22-24 have been amended and claims 27-38 have been added as requested by Applicant in Paper Number 19, filed Dec. 3, 2001.

Claims 1-13 are withdrawn as being drawn to a non-elected invention.

Claims 14, 16-19, 21-24 and 26-38 are currently under examination.

### *Withdrawn Rejections*

2. The rejection of claim 22 under 112 § 2 is withdrawn in view of Applicants' amendment.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 14, 16-19, 21-24 and 26-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The rejection of claims 14, 16, 17, 21 and 24 are maintained as being incomplete method claims, and new claim 27 is added. Applicant has amended the claims to include a step and clarify the method, however the claims are still indefinite as written. The claims encompass a method of screening for a substance that will cause an aberrant receptor to function like a non-aberrant receptor, comprising contacting the aberrant receptor with the substance and determining if the aberrant receptor's activity is similar to the non-aberrant receptor. However,

there are no steps in the claims in which the activity of the non-aberrant receptor is determined either with a normal substrate or the substance to be assayed, so that a comparison cannot be made between the activity of the non-aberrant receptor and the aberrant receptor. There is only a step in which the activity of the aberrant receptor is compared either with or without the substance to be tested, which does not give any information on whether the substance will not activate the non-aberrant receptor.

Claims14, 16, 17, 21, 24 and 27 are also indefinite because for example in claim 27 (4) it recites "comparing the operation activity of the aberrant receptor with the operation activity of the non-aberrant receptor, wherein a change in the operation activity of the aberrant receptor indicates that the substance causes the aberrant receptor to operate", and it is not clear what "**change**" in activity is meant. The assays encompass screening for substances that activate an aberrant receptor, so it is unclear what "change" would be in the aberrant receptor.

The remaining claims are rejected for depending from an indefinite claim.

### *Rejections Over Prior Art*

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4.1 Claims 14, 16-19, 24 and 26 remain rejected and new claims 27-38 are added under 35 U.S.C. 102(b) as being anticipated by Birnbaumer et al., Molecular Endocrinology 8(7):886-894, 1994, for reasons of record in Paper No. 18, pages 2-3.

Applicant traverses the rejection and asserts that Birnbaumer fails to teach every element of the claims, and states that "The present claims are directed to, e.g., a method of screening substances for a substance capable of causing an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, to operate in a manner similar to the non-aberrant receptor". The arginine vasopressin (AVP) of Birnbaumer has substantially changed affinity for the aberrant versus non-aberrant receptor. Applicant further asserts that Birnbaumer fails to teach any method in which the aberrant receptor is brought into contact with a subject substance, and assayed to determine the activity.

Applicants arguments have been considered but are not persuasive. Birnbaumer teaches that cells are transformed with the mutant gene and the wild type gene, that the cells were exposed to AVP, and that the natural ligand AVP stimulated the mutant receptor with an $EC_{50}$ that was increased over wild-type, and the stimulation of the Gs/adenylyl cyclase system (intracellular cAMP) was assessed (pages 887-890). Therefore, Birnbaum anticipates the claims and the rejection is maintained.

4.2 Claim 14 remains rejected under 35 U.S.C. 102(b) as being anticipated by Green et al., J. Biol. Chem. 268(31):23116-23121, 11/5/93, for reasons cited in Paper No. 18, page 3.

Applicant traverses the rejection and asserts that this reference fails to anticipate claim 14, because Green et al. were not using the mutant to screen for compounds that function to restore the operation activity of the aberrant receptor to that of the wild-type receptor, but were seeking to further characterize the mutant receptor.

Applicants arguments have been considered but are not persuasive. Though Green et al. do not specifically state that they were screening for compounds that restore wild-type activity to

the receptor, they were screening for compounds to determine the effect of the compound on activity of the receptor, and found that dopamine (see abstract and Table 1) had the same effect on both the wild-type and mutant receptor. Green et al.'s intent is not at issue; his method anticipates the currently claimed methods as it has all recited method steps and would detect compounds that restore activity. Therefore, Green et al. anticipates the claim and the rejection is maintained.

4.3 Claim 14 remains rejected under 35 U.S.C. 102(b) as being anticipated by Kong et al., J. Biol. Chem. 268(31):23055-23058, 1993, for reasons cited in Paper No. 18, page 3.

Applicant traverses the rejection and asserts that this reference fails to anticipate claim 14, because Kong et al. teaches affinity studies to determine the binding characteristics of the mutant receptor and fails to teach the elements of the presently claimed methods.

Applicant's arguments have been considered but are not persuasive. Though Kong et al. do not specifically state that they were screening for compounds that restore wild-type activity to the mutated δ opioid receptor (D95N), they used a screening method to determine what effects agonists and antagonists had on the mutated receptor compared to the wild-type receptor, and found that the mutated δ opioid receptor (D95N) has reduced affinity for δ receptor-selective agonists and non-peptide agonists compared to wild-type, but has the same affinity for δ receptor-selective antagonists and non-selective opioid agonists. Therefore, Kong et al. screened for compounds that would cause an aberrant receptor, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor (in this case δ receptor-selective agonists and non-peptide agonists), to operate in a manner similar to the non-aberrant

receptor (δ receptor-selective antagonists and non-selective opioid agonists). Therefore, Kong et al. anticipates the claim and the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 14, 16-19, 21-24 and 26 remain rejected, and new claims 27-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lebrun et al., J. Biol Chem. 268(15):11272-11277, 5/25/93, in view of Choong et al., J. Clin. Endocrinol. Metab. 81(1):236-243, 1996, both previously of record, for reasons cited in the previous Office Action, Paper No. 18, at pages 4-5, and below.

New claims 27-38 are rejected over Lebrun et al. in view of Choong et al. Lebrun teaches that the insulin receptor can be assayed for an activity of the receptor, which in the case of insulin is activation of autophosphorylation of the receptor and phosphorylation of substrates. Although the androgen receptor of Choong et al. is a nuclear receptor and does not have a phosphorylation activity or second messenger activity (operation activity) wherein the activity can be assayed by a change in intracellular concentrations of responding substances selected from the group consisting of camp, inositol phosphate and calcium ion, from the teachings of Lebrun, it would be obvious to the ordinary artisan to assay the operation activity of the receptor using an activity of that specific receptor. Since the androgen receptor of Choong et al. is a transcription factor, one way to assay for changes in activity would be using a reporter gene coupled to an androgen receptor-responsive element. Choong et al. teach such a method and

used a reporter plasmid in which the chloramphenicol acetyltransferase (CAT) gene was coupled to the AR-responsive mouse mammary tumor virus (MMTV)-long terminal repeat steroid response element, in order to assay the activities of the mutant and wild-type androgen receptors (see paragraph spanning pages 238-239 and page 241). Therefore, the methods of screening of claims 27-38 are *prima facie* obvious, and the claims are included in the rejection.

Applicant traverses the rejection and asserts that Lebrun does not teach a method of screening for substances, i.e. antibodies, that restore the activation activity of the aberrant receptor, and that Lebrun teaches that the antibodies induce conformational change in the mutant receptor, which is not normally changed by insulin binding, and that the type of mutation in Lebrun is very different from the aberrant receptor used in the presently claimed methods, which has substantially changed affinity for substances that have a natural affinity for a non-aberrant receptor, e.g., natural ligands.

Applicant's arguments have been fully considered but are not deemed persuasive. Although the insulin receptor of Lebrun does not appear to have altered affinity for its natural ligand, insulin, the androgen receptor (AR) of Choong et al. does have reduced binding affinity for mibolerone compared with normal AR. Also, Lebrun does teach a method of screening for compounds that restore the activation activity of the aberrant receptor; Lebrun et al. screened for monoclonal antibodies and found two that restored the receptor kinase activity of the mutant insulin receptor. Therefore, it remains that the combination of Lebrun in view of Choong would lead the ordinary artisan to screen for compounds that would restore wild-type activity to a mutant receptor with altered binding affinity for natural ligand and reduced or no activity.

Applicant further asserts that there is no teaching, suggestion or motivation to use the disclosure of Lebrun to develop a method of screening substances for a substances capable of causing an aberrant receptor to operate in a manner similar to the non-aberrant receptor, and that the goals are different, that the receptor mutation was not in the extracellular, ligand binding portion of the receptor, and that no pharmaceutical composition was prepared. Applicant further asserts that Choong teaches the study of a mutation in the ligand-binding domain of the AR gene which results in reduced ligand binding affinity, and that there is no teaching, suggestion, or motivation to use the receptor or any of the methods described in Choong to develop a method of screening as presently claimed, and that there is simply no motivation for one of ordinary skill in the art to combine Choong with Lebrun to obtain the methods of the present invention, and even if references were combined they clearly would not make the methods of the present invention obvious to one of ordinary skill in the art. Applicant states that "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art."

Applicant's arguments have been fully considered but are not deemed persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Since Choong et al. teach a disease caused by a mutation in the ligand-binding domain of the AR gene in which the binding affinity of the natural ligand is reduced, it would have been *prima facie* obvious to the person of

ordinary skill in the art at the time the invention was made to substitute the mutated AR of Choong et al. in the method of Lebrun et al. for the purpose of finding an antibody that would compensate for the AR mutation. One of ordinary skill in the art would have been motivated to do so by the combined teachings of Choong et al. and Lebrun et al., in order to find an antibody that would compensate for the AR mutation, because the major interest in studying diseases is to discover the cause, and ultimately cures or treatments for the diseases, so as to treat the afflicted individuals, and any such compound found would be formulated in a pharmaceutical composition suitable for administration.

Applicant further asserts that new claims 27-38 are not anticipated or obvious over the cited references, as the Androgen Receptor of Choong et al. is a nuclear receptor and functions by producing a transcription factor after androgen binds to it, and it does not change intracellular concentrations of responding substances selected from the group consisting of camp, inositol phosphate and calcium ion, as claimed in claims 28-38, and therefore the methods of the new claims are not obvious from the cited references.

Applicant's arguments have been fully considered but are not deemed persuasive for reasons set forth above pertaining to the newly introduced claims.

Therefore, all the claims above are rejected under 35 USC § 103.

It is believed that all pertinent arguments have been answered.

***Conclusion***

6. No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 9:00 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Patent Examiner

EBOH 2/22/02

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER